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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,180	10/11/2006	Ken Shortman	19975	4755

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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,180	SHORTMAN ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-29* is/are pending in the application.

4a) Of the above claim(s) *13-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-12,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 26 May 2009.

Claim Status

Claims 1 and 3-29 are pending. New claims 28-29 are added. Claims 1 and 3-6 are amended. However, claims 13-27 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1 and 3-12 are under current examination.

Priority

This application claims benefit as a 371 of PCT/AU04/01840 (filed 12/23/2004) which claims priority from Foreign Application, AUSTRALIA 2003907195 (filed 12/24/2003). The instant application has been granted the benefit date, 24 December 2003, from the Foreign Application, AUSTRALIA 2003907195

RESPONSE TO ARGUMENTS

Claim Objections

The objection to claims 4-6 are objected to under 37 CFR 1.75(c) is withdrawn because of the applicant's claim amendments.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 7-9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maliszewski (Pathol. Biol. 2001; 49: 481-483) for the reasons of record and the comments below.

The applicant's claim amendments and arguments have been fully considered but are unpersuasive.

The claim amendments have narrowed the scope of the claims to administering Flt-3L to a subject. The Maliszewski reference continues to teach this method. Therefore, the claim amendments are not sufficiently persuasive to warrant a withdrawal of the pending rejection.

The applicant presents a discussion contrasting the teachings of Maliszewski and those of the instant application. The applicant's arguments are unpersuasive because the active steps of claim 1 merely comprise "administering to a subject Flt-3L." There are no other active steps required to practice the instant invention. Maliszewski teaches administration of Flt3 Ligand to subjects. On this basis, the examiner has applied the cited art as anticipating the pending claims.

Therefore, the examiner hereby maintains the rejection of claims 1-3 and 7-9 under 35 U.S.C. 102(b) as being anticipated by Maliszewski.

The examiner reiterates the pending rejection:

Claims 1, 3 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Maliszewski (Pathol. Biol. 2001; 49: 481-483).

Claim 1 is directed to a method for preventing onset of an autoimmune disease in a subject said method comprising administering to said subject Flt-3l [Flt-3 Ligand] in an amount effective to increase a sub-type of non-activated, immature and tolerogenic DC selected from Plasmacytoid DC and CD8+ DC or their equivalents thereby inducing or maintaining immune tolerance in said subject. While the examiner has written a lack of enablement for "preventing onset of an autoimmune disease," the examiner applies the art of Maliszewski to the extent that he teaches the method steps of the recited claims. Maliszewski teaches "an approach is to directly expand and/or activate DC *in vivo* using the cytokine Flt3 Ligand" (abstract). Maliszewski teaches "Flt3 Ligand (FL)…can drive large expansion of at least two mouse DC subsets….One DC subset, lymphoid-related DC (LDC), appear to selectively enhance Th1-like immune responses" (page 482, col.1, parag.1). Maliszewski also teaches Flt-3 Ligand may have its greatest effects when combined with cytokines…[thereby] increasing the ability of FL-expanded DCs to stimulate CD8+ T cells" (page 482, col.1 bridging col.2). Additionally, Maliszewski indicates this type of therapy is useful for treatment of autoimmunity (page 482, col.2, last parag.). Maliszewski teaches administration of Flt-3 Ligand.

Claim 3 is directed to the method of claim 1 wherein the Flt-3L is co-administered with a cytokine. Maliszewski also teaches Flt-3 Ligand may have its greatest effects when combined with cytokines" (page 482, col.1).

Claim 7 is directed to the method of claim 1 wherein the subject is a human, non-human primate, livestock animal, laboratory test animal, a companion animal, a captured wild animal or an avian species. Maliszewski is a review article which cites models applied to a laboratory mouse and humans.

Claim 8 is directed to the method of claim 7, wherein the subject is a human. Maliszewski is a review article which cites applying their method to humans.

Claim 9 is directed to the method of claim 1, wherein the Flt-3L is derived from the same species to which it is administered. In particular, Maliszewski is a review article which cites models where the Flt-3L is derived from the same species to which it is administered.

Accordingly, Maliszewski anticipates each of the specific limitations of the instant claims. It is acknowledged that Maliszewski does not specifically teach that this would result in preventing the onset of an autoimmune disease in a subject as set forth in the preamble of the instant claim, but because the teachings of Maliszewski provide the same method step, any outcome of practicing this step would naturally flow from the method.

35 USC § 112, 1st paragraph (enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-12 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record and the comments below.

The applicant's claim amendments and arguments have been fully considered but are unpersuasive.

The claim amendments have narrowed the scope of the claims to administering Flt-3L to a subject. The claims no longer contain mention of administering "Flt-3/Flt-3L receptor agonist;" therefore, the portions of the lack of enablement rejection directed to this embodiment is moot. These sections have been removed from the reiteration of the rejection below. Although this portion of the rejection is no longer relevant, there is sufficient reason to maintain the other rationales for lack of enablement. Therefore, these claim amendments are insufficient to overcome the rejection as a whole.

In addition, the applicant argues that Example 12 demonstrates "prevention of the onset of diabetes is achieved" (Remarks, filed 5/26/2009, page 10, lines 12-13). Example 12 states, "repeated administration of mFL had the predicted effect of preventing diabetes development completely…by 300 days of age" (Spec. Example 12, page 44, lines 24-25). Example 3 indicates that "[m]ice were considered diabetic if blood glucose was above 11 mM on two successive days" (Spec. page 38, lines 3-4). The examiner notes that Example 12 uses NOD mice and demonstrates numerous different times of administrating murine Flt3L which did not prevent diabetes (see page 44, lines 5-16). Furthermore, based upon the language of Examples 2 and 12, it seems that the animals of Example 12 asserted to have been prevented from developing

diabetes had received 10 µg of Flt3L per day for 10 consecutive days during the periods days 20-29, 50-59 and 100-109 post birth. Therefore, the specification seems to provide support for "a method for preventing blood glucose above 11 mM on two successive days in a NOD mouse, comprising administering to said mouse 10 µg of Flt3L per day for 10 consecutive days during each of the periods after birth consisting of days 20-29, days 50-59 and days 100-109." Since the foundation of the specification's statement regarding "repeated administration of mFL…preventing diabetes" (Spec. Example 12, page 44, lines 24-25) is based solely on elevated blood sugar and does not correlate to an equivalent destruction of islet cells, the examiner must consider the teachings of the specification together with the teachings of the art. After the filing of the application, there has been no recognition that administration of Flt3 ligand is sufficient to prevent Type I diabetes. In fact, post-filing literature indicates that Type I Diabetes cannot be prevented. Therefore, the specification seems to support delaying some of the complications related to type 1 diabetes (e.g., hyperglycemia). The specification seems to show that hyperglycemia can be delayed or prevented through administration of Flt3L during a particular regime of administration over a 100 day period in NOD mice. However, this is not the same a preventing onset of the disease itself.

In addition, Example 12 does not apply to any other autoimmune diseases other than mouse models of type I diabetes. So, the examiner concludes that the claims have not been enabled for the full scope of preventing onset of autoimmune diseases by administration of Flt3L.

Furthermore, the applicant has provided two references to support the enabling disclosure of the instant claims. The applicant asserts that Steinman et al. (PNAS. Jan. 8, 2002; 99(1): 351-358) and Heath et al. (Nature. 2001; 1: 126-135) confirm that administration of Flt3 Ligand to NOD model delays or prevents onset of autoimmune disease (Remarks, page 10, top paragraph, filed 5/26/2009). The applicant refers the examiner to Steinman, page 353 to support this assertion. The examiner could not find any mention of Flt3 Ligand administration on page 353 of Steinman. The applicant refers the examiner to Heath, Figure 4, to support this assertion. The examiner could not find any mention of Flt3 Ligand administration in Figure 4 of Heath. Therefore, the examiner finds these Exhibits unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 1 and 3-12 remain rejected under 35 U.S.C. 112, first paragraph (lack of enablement). In addition, because claims 28-29 are also encompassed by the pending lack of enablement rejection, the examiner hereby extends the pending rejection to encompass claims 28-29.

The examiner reiterates the pending rejection:

Claims 1, 3-12 and 28-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

NATURE OF THE INVENTION

The breadth of the claims encompasses methods of preventing onset of a large genus of autoimmune diseases.

The specification (and claim 11) indicate that particular autoimmune diseases encompassed by the method of prevention can be: Active Chronic Hepatitis, Addison's Disease, Anti-phospholipid Syndrome, Atopic Allergy, Autoimmune Atrophic Gastritis, Achlorhydra Autoimmune, Celiac Disease, Crohns Disease, Cushings Syndrome,

Dermatomyositis, Type I Diabetes, Discoid Lupus, Erythematosis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's Thyroiditis, Idiopathic Adrenal Atrophy, Idiopathic Thrombocytopenia, Insulin-dependent Diabetes, Lambert-Eaton Syndrome, Lupoid Hepatitis, Lymphopenia, Mixed Connective Tissue Disease, Multiple Sclerosis, Pemphigoid, Pemphigus Vulgaris, Pernicious Anema, Phacogenic Uveitis, Polyarteritis Nodosa, Polyglandular Auto. Syndromes, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Psoriasis, Raynauds, Reiter's Syndrome, Relapsing Polychondritis, Rheumatoid Arthritis, Schmidt's Syndrome, Scleroderma - CREST, Sjogren's Syndrome, Sympathetic Ophthalmia, Systemic Lupus Erythematosis, Takayasu's Arteritis, Temporal Arteritis, Thyrotoxicosis, Type B Insulin Resistance, Ulcerative Colitis and Wegener's Granulomatosis. More particularly, claim 12 indicates that autoimmune (Type-1) diabetes can be prevented by the claimed method.

GUIDANCE & WORKING EXAMPLES

The specification does not provide guidance for or working examples for preventing onset of autoimmune diseases. The focus of the working examples is directed to murine diabetic mouse models. The working examples utilize Non-Obese Diabetic (NOD) which is known as an animal model for type 1 diabetes. Non-obese diabetic (NOD) mice exhibit a susceptibility to spontaneous development of autoimmune insulin dependent diabetes mellitus (IDDM). No working examples are provided which encompass the larger genus of autoimmune diseases described in claim 11, beyond the limited experiments on NOD mice.

In the NOD mice experiments, the applicants determined whether an animal had become diabetic by measuring urine and blood sugar levels (Example 3). Throughout their experiments (Figs. 4 & 5; Examples 12 & 14), the inventors indicated that some NOD mice which were treated with Flt-3L were not diabetic after certain days of treatment. The examiner points out that the claims are directed to prevention of autoimmune disease and not to lack of blood sugar. The specification indicates that at the end of the experiments, histological sections of pancreas were taken from both diabetic and non-diabetic mice. The specification indicates "[s]ome insulitis (mononuclear cell invasion of the pancreas) was seen in the protected, Flt-3L treated mice, but destruction of β-cells was markedly reduced" (page 47, lines 28-29). The specification asserts that onset of diabetes was achieved after several 10-day treatments of Flt-3L; however, since there are histological evidence of autoimmune effect, the examiner concludes that a skilled artisan would interpret this evidence as indicating the autoimmune disease was not prevented. In addition, the specification states, "there was no reduction in diabetes incidence; the onset of diabetes was simply delayed" (page 48, lines 18-19). So, the examples of the instant specification cannot support claims for "preventing onset of an autoimmune disease."

In addition, for the sake of compact prosecution, the examiner is addressing methods comprising co-administration of Flt-3 ligand and a Toll-like receptor (as in claims 4-6). Example 6 of the instant specification shows an *in vitro* method in which dendritic cells are cultured with the Toll-like receptor 9 agonist, oligo-CpG. However, this is not an example of a method comprising co-administration of Flt-3L and Toll-like

receptor (as in claims 4-6). In addition, Rifkin et al. (Immunological Reviews 2005; 204: 27-42) suggest that Toll-like receptor ligands may play a role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus. Because the prior art indicated that administration of Toll-like receptor ligands induces autoimmune diseases encompassed by the instant claims, notably systemic lupus erythematosus (recited in claim 11), the examiner concludes that there is some unpredictability in making and using the claimed invention.

The absence of working examples directed to preventing onset of autoimmune diseases necessitates further experimentation. Therefore, the specification does not provide sufficient guidance on how to make and use the instantly claimed invention.

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

The state of the art teaches that prevention of autoimmune diseases (and in particular autoimmune diabetes) is not a highly successful technique or has highly variable results.

Diabetes mellitus type 1 (type I diabetes, T1D, T1DM, IDDM, juvenile diabetes) is a form of diabetes mellitus. Type 1 diabetes is an autoimmune disease that results in destruction of insulin-producing beta cells of the pancreas. Numerous sources indicate that there is currently no clinically useful preventive measure against developing type 1 diabetes. In particular, WebMD states, “Currently there is no way to prevent type 1 diabetes” (http://diabetes.webmd.com/tc/type-1-diabetes-prevention ; last updated November 21, 2006). Most of the currently available art indicates that some of the

complications related to type 1 diabetes, such as eye, kidney, heart, blood vessel and nerves diseases can be delayed or prevented through various treatments. However, this is not the same a preventing onset of the disease itself.

In addition, regarding claims 9-10, directed to wherein the Flt-3L is derived from the same or different species to which it is administered, the specification indicates that there is some variation in results which makes practicing the claimed method somewhat unpredictable.

Consequently, there is ample reason to conclude that there would be a high degree of unpredictability in practicing the instant invention and undue amount of experimentation would be required to make and use the instant invention.

CONCLUSION

In conclusion, given the breadth of the claims, the limited scope of the specification, and state of the art, an undue quantity of experimentation is require to make and use the invention.

Allowable Subject Matter

The examiner believes that the breadth of the preamble and the simplicity of the active method steps present obstacles for patenting the inventive feature of the instant application. Throughout the applicant's arguments, he has stressed the importance of the effect of Flt3L on the maturation of dendritic cells and the nexus of this to treating the symptoms of type I diabetes. The examiner hopes the applicant can try to focus claim amendments on better capturing this feature.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Joseph T. Woitach/
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